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Editorial

Switching of Antiepileptic Drug Formulations

J. Nile Barnes, PharmD and Karen L Rascati, PhD

Departments of Pharmacy Administration, The University of Texas College of Pharmacy, Austin, Texas

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"The Controversy over Generic Antiepileptic Drugs",[1] which appears in this issue, reviews bioequivalence test procedures of antiepileptic drug (AED) formulations. This review, by Shaw and Hartman, points out the variability in the pharmacokinetic properties of many AED formulations. They conclude that drug concentrations between the standard brand name formulation and any one generic product are likely to be minimal, but generic-to-generic comparisons are more likely to produce clinically important differences. While these different formulations may be clinically relevant to only a small percent of patients, a seizure can have a substantial impact on a patient's life. The authors encourage more studies on the bioequivalence of AEDs to help mitigate the potential pitfalls of medication switching, especially in the subset of patients who may be more sensitive to narrow changes in drug availability.

see related articles on pages 66 and 81

Questions raised by the Shaw and Hartman review revolve around the applicability of the current standard for bioequivalence to narrow therapeutic index (NTI) drugs. The current Food Drug Administration and European Medicines Agency standards, while generally strict, are not designed for NTI drugs. Should this issue be revisited? Should the pharmacokinetic parameters for NTI drugs be tighter? This may make generics more difficult to manufacture, but ultimately could provide less expensive alternatives to brands that minimize the adverse events associated with switching

ABBREVIATIONS AED, anti-epileptic drug; NDC, National Drug Code; NTI, narrow therapeutic index

Other information on the effects of AED switching recently appeared in the literature.[2-4] Three studies used large nationwide databases containing patient medical claims to address this issue.[2-4] Zachry et al.[2] used data from the Ingeneix Database; Rascati et al.[3] used data from PharmMetrics; and Hansen et al.[4] used data from the MarketScan database. These three studies used case-control analyses to determine the probability of having an epilepsy-related event requiring acute care (e.g., ambulance, emergency department, or hospitalization services with a primary diagnosis of epilepsy) for patients who had a recent switch in the formulation of their AED (brand-to-generic, generic-to-brand, or generic-to-generic) compared to those with no switch. After adjusting for baseline differences in the cohorts, all three studies found a significant increase in events for those who had a formulation switch compared to those who did not have a switch [Zachry et al. OR = 1.81 (95% CI, 1.25-2.63); Rascati et al. OR = 1.84 (95% CI, 1.44-2.36); and Hansen et al. OR = 1.57 (95% CI, 1.17-2.10)]. While retrospective case-control studies have limitations (e.g., potential selection bias), results from these studies add important information based on data obtained from a large number of patients. This method is useful when it is not feasible to conduct a large randomized controlled trial.

Address correspondence to: Karen L. Rascati, PhD, Eckerd/Turley Centennial Endowed Professor, Pharmacy Administration, College of Pharmacy, The University of Texas at Austin 1 University Station, PHR 3.210, Austin, TX, 78712-0127, email: krascati@mail.utexas.edu

In 2009, *Medical Letter* consultants revisited their advice on generic substitution. After reviewing the evidence available, they recommended generic substitution for most medications, but their recommendation for levothyroxine and AEDs is "Use one formulation (brand or generic) consistently or, if consistency is not possible with generics, prescribing the brand name routinely".[5]

Based on both pharmacokinetic and retrospective studies on AED switching, it seems that caution is warranted. Of course, our goal as healthcare providers includes minimizing or eliminating morbidity and mortality. The potentially catastrophic nature of breakthrough seizures is more than simply troubling to patients.

Currently, the primary method for reducing the switch-induced adverse consequences of a medication with a NTI has been what the safety industry terms a "work around." In this case we mean the "DO NOT SUBSTITUTE" or "BRAND MEDICALLY NECESSARY" words on the prescription. While this eliminates the pharmacokinetic problems associated with AED switching (and other NTI switching), it ignores the cost savings associated with the use of generic formulations. This loss of savings affects patients, payers and society as a whole.

Rather than encourage this "work around," re-tooling the prescribing and dispensing steps is essential to allow for specific generic selection. Not that the initial selection appears to be especially important, but that the continuation of therapy demands it. The key to a better solution is already available to pharmacists—the National Drug Code (NDC)*. NDC codes are specific to formulation—no two products have the same NDC. Retail pharmacies currently have the ability to track NDC numbers of each product dispensed; it would be a small additional automated step to ensure a patient was not switched to a different generic product.

Another important step is to ensure the supply chain is uninterrupted. Pharmacy buyers (not always pharmacists) from independent pharmacies, chain retail pharmacies and wholesale distributors must stock the same generics every month and not simply buy the least expensive product each time. Obviously, there will be switches occasionally: periodic contract changes, patients changing pharmacies due to relocation. But if we educate the prescribers, pharmacists, technicians, and buyers—the problem can be minimized.

The stakeholders in this issue are numerous—patients, physicians, pharmacists, drug wholesalers, and pharmaceutical companies are just the tip of the iceberg. Society as a whole has an interest in solving this dilemma. Clearly, more research should be conducted regarding the pharmacokinetics of NTI drugs; policy changes should be considered; and in the interim, NDC tracking should be implemented.

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*NDC codes - Drug products are identified and reported using a unique, three-segment number, called the National Drug Code (NDC), which is a universal product identifier for human drugs."Drug products are identified and reported using a unique, three-segment number, called the National Drug Code (NDC), which is a universal product identifier for human drugs. The first segment, the labeler code, is 4 or 5 digits long and assigned by the Food and Drug Administration (FDA) upon submission of a Labeler Code Request. A labeler is any firm that manufactures, repacks or distributes a drug product. The second segment, the product segment, is 3 or 4 digits long and identifies a specific strength, dosage form, and formulation for a particular firm. The third segment, the package segment, is 1 or 2 digits long and identifies package forms and sizes. In very exceptional cases, product and package segments have contained characters other than digits.

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